REMARKS

Claims 53-60, 63-74, and 81-99 are pending in this application. Claims 53 and 95 have been amended. No new matter has been added by these amendments, and their entry is respectfully requested.

Applicants acknowledge, with thanks, the Examiner's entry of the claim amendments from the Response filed January 2, 2009.

Rejections under 35 U.S.C. § 102(b)

Claims 53, 55, 57, 63, 65, 67, 69, 71, 73, 81-85, 87, 89, 91, 92, 95, 96, and 99 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mivechi *Cancer Research* 49:1954-58 (1989) ("*Mivechi*") as evidenced by Lozzio and Lozzio *Blood* 45:321-34 (1975) ("*Lozzio*"). The Examiner continues to allege that the cell lysates reported in *Mivechi* anticipate the cell lysate of the prior claims. Specifically, the Examiner asserts that, in view of page 22 of the present application, the K562 cells described in *Mivechi* are NM-F9 and NM-D4 cells and concludes that *Mivechi's* lysate from these cells would comprise lysate "obtainable" by lysing cells so as to obtain a lysate that is capable of inducing a humoral immune response against TF antigen. Advisory Action at 2. Applicants traverse.

It is well-established that for a prior art reference to anticipate a claim under 35 U.S.C. § 102, it must teach every element of the claim. M.P.E.P. § 2131. Applicants' claims are drawn to products obtainable by inducing necrosis of TF-expressing NM-F9 (Accession No. DSM ACC 2606) or NM-D4 (Accession No. DSM ACC 2605) tumor cells

and then obtaining a lysate from the cells. There is no question that applicant's claims require 1) that the claimed lysate must be the same as the lysate from the specific cell lines recited and 2) that the claimed lysate must be capable of inducing a humoral immune response against the TF antigen. In contrast, the cell preparation of *Mivechi* is obtained from cells that, although perhaps have a common evolutionary origin to those recited in the pending claims, are nevertheless different cells. This is clearly evidenced, at least in part, by the fact that, in contrast to both NM-F9 and NM-D4 cells, K562 cells *do not express the TF antigen*. *See*, for example paragraph [0127] and Figure 1 of U.S. Patent Application Publication No. 2006/0292129, corresponding to co-pending USSN 10/568,098. Thus, no lysate from these cells will be capable of producing a humoral immune response against the TF antigen, as required by the claims. NM-F9 and NM-D4 cells were derived from a parental population of K562 cells by mutagenizing them and selecting for cells with constitutive high-level expression of TF antigen. *See* paragraphs [0109] and [0110] of the 2006/0292129 publication (further describing how NM-F9 cells were generated by selecting EMS-mutagenized K562 cells for stable TF-expression and NM-D4 cells were selected from NM-F9 cells after further treatment and selection for MUC1 expression). If this feature did not distinguish NM-F9 and NM-D4 cells from K562 cells, no such selection would be possible.

The Examiner continues to point to page 22 of the specification to support the contention that K562 cells, as described in *Mavechi*, are NM-F9 and NM-D4 cells. The passage reads "[t]he term "NM-F9" (also referred herein as "F9" or "TF-positive NM-F9 cells") or "NM-D4" means cell lines or cells derived from the human myelogenous

leukemia cell line K562. (ATCC: CCL-243)." Even in isolation, however, this passage states only that NM-F9 and NM-D4 cells were *derived* from K562 cells. This passage does not teach or suggest that K562 cells are equivalent to NM-F9 or NM-D4 cells or that they possess the ability to express TF antigen sufficient to produce a humoral response. Instead, this passage merely clarifies the evolutionary origin of the NM-F9 and NM-D4 cells referenced in the application. Furthermore, the paragraph preceding this passage makes clear that the terms NM-F9 and NM-D4 have very specific meaning (i.e., particular depository accession numbers, as recited in Applicants' claims): "[i]n a preferred embodiment, the tumor cells used for the production of a cell lysate as described herein are NM-F9 (DSMZ deposit No. DSM ACC2606 or NM-D4 cells (DSMZ deposit No. DSM ACC2605)."

Thus, when read in proper context, the passage referenced by the Examiner simply points out that, although NM-F9 and NM-D4 cells were derived from K562 cells, they are distinct cells that possess an important phenotype that is clearly absent from K562 cells, namely stable TF antigen expression. The fact that K562 cells may contain chromosome abnormalities, as evidenced by *Lozzio*, does not change these facts or the inadequacy of *Mavechi* to anticipate the claims. Importantly, Applicants teach that lysates of NM-F9 cells, when prepared by the methods of the invention, induced IgG immune responses in two different strains of mice. See Tables 2 and 3, which show that 3/3 mice in each of the two strains tested (thus 6/6 mice, total) have antigen specific IgG immune response to TF antigen.

The Examiner offers absolutely no explanation for how a cell line (K562) that does not express TF antigen (*see* Figure 1 of Publication No. 2006/0292129) could produce a cell lysate capable of inducing a humoral immune response against the absent TF antigen. Applicants respectfully submit that it is a matter of basic logic and biochemistry that cells that do not contain a particular complex antigen *cannot* then produce lysates containing the antigen unless they are altered to do so. There is no evidence in the art that teaches or suggests such an alteration. The fact that NM-F9 and NM-D4 cells were derived from K562 cells and may possess some similar characteristics is wholly inadequate to anticipate the pending claims. K562 cells are not NM-F9 (Accession No. DSM ACC 2606) or NM-D4 (Accession No. DSM ACC 2605) cells and, because K562 cells do not express the TF antigen, they cannot then be used to obtain a lysate that is capable of inducing a humoral immune response against TF antigen, as required by the pending claims. Thus, *Mivechi* does not teach all elements of Applicants' claims and does not anticipate them. Accordingly, the rejection should be withdrawn and the claims reconsidered.

Rejections under 35 U.S.C. § 103(a)

The Examiner maintains two separate rejections of Applicants' claims under 35 U.S.C. § 103(a). Applicants note at the outset, however, that the collective disclosure of the references cited in these rejections share the same critical defects as *Mivechi*, above, and consequently, do not render Applicants' claims obvious. Specifically, these rejections are based on the mistaken allegation that K562 cells are the same as NM-F9

and NM-D4 cells as defined by a passage on page 22 of the specification (which corresponds to paragraph [0078] of U.S. Patent Application Publication No. 2006/0127419). The Examiner alleges that K562 cells can produce lysate capable of inducing a humoral immune response against TF antigen, despite the fact that K562 cells do not express the TF antigen. However, the Examiner has provided no evidence to support this assertion. There is no question that Applicants' claims require that the lysate must be capable of inducing a humoral immune response against the TF antigen. Applicants submit that no valid standard of obviousness can support these rejections since, alone or in combination, the cited references fail to teach or suggest these essential features of the claims and certainly do not provide the requisite reasonable expectation of success. *See* M.P.E.P. § 2143.02. To facilitate prosecution, however, Applicants address the rejections in turn.

I. *Subjeck* in view of *Yoshima*

Claims 53-60, 67-74, 81-83, 86, and 91-99 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Subjeck et al. (U.S. Patent No. 6,984,384) ("*Subjeck*"), in view of Yoshima et al., *J. Biol. Chem.* 273:25466-71 (1998) ("*Yoshima*"). The Examiner maintains the assertion that *Subjeck* discloses a lysate of mutated tumor cells obtainable by inducing necrosis by heat treatment and lysing the necrotic tumor cells, although the Examiner acknowledges that *Subjeck* does not teach NM-F9 or NM-D4 cells, or percentages of cells that are necrotic or express HSP70. The Examiner relies on *Yoshima* to allegedly describe NM-F9 or NM-D4 cells that one of skill in the art

would supposedly be motivated to use as the mutated tumor cells of *Subjeck*. Applicants traverse.

Applicants first note that *Subjeck* does not teach inducing necrosis in *any* cells. The passage relied on by the Examiner (column 19) merely states temperature treatments that can be used to *stress* tumor cells or infected cells prior to peptide purification, in order to enhance binding of immunogenic peptide to stress polypeptide. *Subjeck* at column 19, lines 42-45. This passage, and indeed the entirety of *Subjeck* does not teach inducing necrosis in any cells. *Subjeck* merely discloses immunogenic polypeptides that can be isolated from mutated tumor cells and, as acknowledged by the Examiner, does not teach lysates using NM-F9 or NM-D4 tumor cells. *Yoshima's* report of K562 cells, which are further genetically engineered to contain an HSP70 transcriptional reporter system, does not remedy these defects.

As discussed above and demonstrated in Applicants' copending application USSN 10/568,098 (Publication No. 2006/0292129), NM-F9 and NM-D4 cells are not K562 cells. Rather, they are derived from mutagenized K562 cells and were selected for their ability to strongly and stably express the tumor-specific TF antigen, a property that K562 cells do not possess.

Yoshima's K562 cells are transfected with a reporter system for HSP70 transcription. The Examiner states that these transfected cells *are* NM-F9 and NM-D4 cells based on the definition of these cells as "derived from the human myelogenous leukemia cell line K562" in the specification (page 22; paragraph [0079] in Publication No. 2006/0127419). Again, the specification indicates that the NM-F9 and NM-D4 cells

recited in the claims are TF-positive. Nothing in *Yoshima* suggests that the introduction of an HSP70 reporter system into K562 cells or the induction of HSP70 by an artificial HSF1 construct in response to hemin treatment would induce the cells to express the TF antigen, let alone produce a lysate capable of inducing a humoral immune response to TF antigen. A skilled artisan would not have any reason to predict that it would—HSP70 and TF are completely different antigens. Moreover, Applicants' disclosure provides strong evidence to the contrary. Tables 2 and 3 in the specification teach that even lysates of TF-expressing NM-F9 cells, when treated to express elevated levels of HSP70, did not elicit humoral immune responses to TF antigen in mice. In contrast, necrotic lysates of these cells do give rise to strong humoral immune responses to TF antigen. Applicants submit that there is no basis to believe that *Yoshima's* K562 cells express TF antigen, let alone produce lysate able to elicit a humoral response to this antigen. Thus, *Yoshima* does not remedy the defects of *Subjeck* and their collective disclosures cannot render the pending claims obvious. Accordingly, Applicants request withdrawal of this rejection.

II. *Mivechi* in view of *Subjeck*

Claims 53-60, 63-74, and 81-99 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over *Mivechi* as applied above, further in view of *Subjeck*. Specifically, the Examiner alleges that one of ordinary skill in the art would have been motivated to use the NM-F9 and NM-D4 cells purportedly used by *Mivechi* as the mutated tumor cells for producing the vaccine disclosed by *Subjeck*. Applicants traverse.

As described above, *Mivechi* discloses K562 cells. K562 cells are distinct from NM-F9 or NM-D4 cells in that they do not express the TF antigen, and therefore, when lysed, cannot elicit a humoral immune response against the TF antigen. *Subjeck* does not remedy these defects, since it only teaches preparations of immunogenic polypeptides that can be isolated from mutated tumor cells, which can optionally be applied to dendritic cells. *Subjeck* does not teach NM-F9, NM-D4 cells, or any other cells expressing TF antigen. Because the collective disclosure of *Mivechi* and *Subjeck* contains no teaching, suggestion, or motivation to generate lysates obtainable from NM-F9 (Accession No. DSM ACC 2606) or NM-D4 (Accession No. DSM ACC 2605) cells that are capable of eliciting a humoral immune response against the TF antigen, it does not render the claims obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

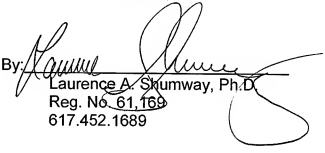
In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and timely allowance of the claims. Applicants invite the Examiner to call the undersigned Applicants' representative with any questions or comments.

Please grant any additional extensions of time required to enter this response and charge any additional fees to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 1, 2009

By: 
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